Short Communication

Aspirin Use and Risk of Biliary Tract Cancer: A Population-Based Study in Shanghai, China

Enju Liu,[1] Lori C. Sakoda,[2] Yu-Tang Gao,[1] Asif Rashid,[3] Ming-Chang Shen,[4] Bing-Sheng Wang,[5] Jie Deng,[1] Tian-Quan Han,[6] Bai-He Zhang,[7] Joseph F. Fraumeni Jr.,[2] and Ann W. Hsing[2]

[1]Shanghai Cancer Institute, Shanghai, China; [2]Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland; [3]Department of Pathology, MD Anderson Cancer Center, Houston, Texas; [4]Shanghai Tumor Hospital and [5]Zhongshan Hospital, Fudan University, Shanghai, China; [6]Department of Surgery, Ruijin Hospital, Shanghai Second Medical University, Shanghai, China; [7]Institute of Oriental Hepatobiliary Surgery, Shanghai Second Military University, Shanghai, China

Abstract

The association of gallbladder and bile duct cancers with gallstones, cholecystitis, and cholangitis suggest that chronic inflammation contributes to the carcinogenic process. However, the effect of nonsteroidal anti-inflammatory drugs, such as aspirin, on biliary tract cancer has not been well studied. In a population-based case-control study conducted in Shanghai, China, we examined the relationship between aspirin use and the risk of biliary disease. A total of 627 patients with biliary tract cancer, including cancers of the gallbladder (n = 368), extrahepatic bile duct (n = 191), and ampulla of Vater (n = 68); 1,037 patients with biliary stones; and 958 healthy adults were included in the study. Self-reported data on aspirin use was collected from study participants by in-person interview. The prevalence of aspirin use was low, with 5.7% of the population controls being regular users. After controlling for age, sex, education, and biliary stone status, aspirin use was associated with a reduced risk of gallbladder cancer [odds ratio (OR), 0.37; 95% confidence interval (CI), 0.17-0.88]. An inverse relationship was also observed for frequency and duration of use and with younger age when starting use. In addition, there was a nonsignificant reduction in the risk of bile duct (OR, 0.48; 95% CI, 0.19-1.19) and ampullary cancers (OR, 0.22; 95% CI, 0.03-1.65) associated with aspirin use, whereas no clear association was seen with biliary stones (OR, 0.92; 95% CI, 0.59-1.44). Further studies of biliary tract cancer in other populations are needed to confirm these results and to elucidate the mechanisms that underlie the reduced risk associated with use of aspirin and possibly other nonsteroidal anti-inflammatory drugs. (Cancer Epidemiol Biomarkers Prev 2005;14(5):1315–8)

Introduction

Regular use of aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) has been associated with lower risk of colorectal adenomas and cancer (1), and to some extent with other cancers, including the stomach, esophagus, breast, lung, ovary, prostate, and bladder (2). Limited data are available on the relationship of NSAID use with biliary tract cancer, which encompasses tumors of the gallbladder, extrahepatic bile ducts, and ampulla of Vater. Although the etiology of these uncommon, but often fatal, tumors is not well understood, it has been suggested that chronic inflammation plays a critical role given the strong and consistent link of gallstones and cholecystitis with gallbladder cancer (3) and of primary sclerosing cholangitis with bile duct cancer (4). To determine whether NSAID use might confer reduced risk for biliary disease, we examined the association of aspirin use with the risk of biliary tract cancer and biliary stones in a population-based case-control study conducted in Shanghai, China, where the incidence of biliary tract cancer has increased sharply in recent years (5).

Received 1/17/05; revised 2/28/05; accepted 3/14/05.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Note: E. Liu and L.C. Sakoda contributed equally to this work.

Requests for reprints: Ann Hsing, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Department of Health and Human Services, 6120 Executive Boulevard, EPS 7058, Bethesda, MD 20892-7234. Phone: 301-496-1691; Fax: 301-402-0916. E-mail: hsinga@mail.nih.gov

Materials and Methods

Study Population. Individuals of ages 35 to 74, who were newly diagnosed with biliary tract cancer between June 1997 and May 2001, were identified using a rapid reporting system established across 42 collaborating hospitals that was effective in capturing over 95% of all eligible cases of biliary tract cancer in urban Shanghai during the study period. A total of 627 cancer patients (368 gallbladder, 191 extrahepatic bile duct, and 68 ampulla of Vater), whose diagnoses were confirmed by expert review of histology slides and/or data from computed tomography scan, magnetic resonance imaging, abdominal ultrasound, and endoscopic retrograde cholangiopancreatography, and 1,037 patients with biliary tract stones, frequency matched to the cancer cases on age, sex, and hospital, were enrolled in the study. These two case groups were included to permit assessment and identification of unique and shared risk factors associated with biliary tract cancer and biliary stones. From all permanent Shanghai residents listed in the Shanghai Resident Registry, individuals without a history of cancer were randomly selected as controls by frequency matching to the cancer cases on age and sex. Of the 1,164 eligible population controls selected, 959 (82%) agreed to participate. The Institutional Review Boards of the U.S. National Cancer Institute and the Shanghai Cancer Institute approved the study protocol. All participants provided written informed consent.

Data Collection. Each participant was interviewed in person by a trained interviewer using a structured questionnaire to collect information on demographic factors; consumption of cigarettes, alcohol, and tea; medical history; family history of

Table 1. Percent distribution of selected characteristics by case-control status

Characteristic	Population controls		Cancer cases			Biliary stone cases (n = 1,037)
	All (n = 959)	No biliary stones (n = 735)	Gallbladder (n = 368)	Extrahepatic bile duct (n = 191)	Ampulla of Vater (n = 68)	
Sex, %						
Male	39	43	27*	52†	54†	38‡
Female	61	57	73	48	46	62
Age at interview, %						
<55	13	16	13	15	9	29‡
55-64	28	28	26	25	29	29
≥65	59	56	61	60	62	42
Marital status, %						
Single	1	1	1	1	0	1‡
Married	78	80	77	84	81	85
Separated/divorced	2	2	1	1	1	1
Widowed	18	17	21	14	18	13
Education, %						
None/primary	41	39	54*	45	43	30‡
Junior middle	24	24	21	23	23	28
Senior middle	20	21	14	16	22	24
Some college and above	15	16	11	16	12	18
Body mass index (kg/m^2), %						
Q1: <20.8	25	28	17*	26	24	16‡
Q2: 20.8-22.8	25	26	23	23	20	21
Q3: 22.9-25.4	25	24	26	31	25	33
Q4: ≥25.4	25	21	34	20	31	30
Biliary stones, %	23	0	81*	63†	49†	100‡
History of diabetes, %	8	6	14*	10	7	11‡
History of hypertension, %	42	40	37	32†	29†	33‡
Cigarette use, %	30	31	24*	40†	44†	27
Alcohol consumption, %	21	23	14*	26	22	16‡
Tea consumption, %	59	57	73*	58	57	60

*Compared with population controls without prior cholecystectomy, $P < 0.05$.
† Compared with population controls, $P < 0.05$.
‡ Compared with population controls without biliary stones, $P < 0.05$.

cancer; reproductive history and exogenous hormone use (females only); diet; physical development and activity; and occupation. The section on medical history elicited information on whether subjects had ever taken aspirin at least twice a week for longer than a month 1 year before interview. When aspirin use was reported, subsequent questions were asked to ascertain the age when regular use started and stopped, average number of pills taken per week, and duration of use. All interviews were tape recorded and reviewed to ensure that the interviews were conducted uniformly among participants and that the data were recorded accurately. Five percent of the study population was randomly selected for reinterview within 3 months to assess reproducibility of the interview data. Concordance between the two interviews on responses to key questions was >90%.

Status for biliary stones (located in the gallbladder or bile ducts) was determined for cases using data collected from clinical diagnostic work (abdominal ultrasound, computed tomography scan, magnetic resonance imaging, and/or endoscopic

Table 2. ORs and 95% CIs for biliary tract cancer (by anatomic subsite) and biliary stones in relation to aspirin use

	Population controls			Cancer cases	
	All	Without cholecystectomy	Without stones	Gallbladder	
	n (%)	n (%)	n (%)	n (%)	OR* (95% CI)
Aspirin use‡					
Never	903 (94.3)	847 (94.0)	696 (94.7)	356 (97.0)	1.00
Ever	55 (5.7)	54 (6.0)	39 (5.3)	11 (3.0)	0.37 (0.17-0.80)
Former	29 (3.0)	28 (3.1)	23 (3.1)	7 (1.9)	0.57 (0.21-1.57)
Current	26 (2.7)	26 (2.9)	16 (2.2)	4 (1.1)	0.23 (0.07-0.74)
Age at first use (y)					
≤60	28 (2.9)	28 (3.1)	19 (2.6)	4 (1.1)	0.22 (0.07-0.71)
>60	27 (2.8)	26 (2.9)	20 (2.7)	7 (1.9)	0.58 (0.21-1.59)
Frequency of use (pills/wk)					
≤7	42 (4.4)	41 (4.6)	30 (4.1)	9 (2.5)	0.42 (0.18-0.99)
>7	11 (1.2)	11 (1.2)	8 (1.1)	2 (0.5)	0.32 (0.06-1.80)
					P_{trend} = 0.02
Duration of use (mo)					
≤6	23 (2.4)	22 (2.4)	19 (2.6)	4 (1.1)	0.45 (0.12-1.62)
>6	32 (3.3)	32 (3.6)	20 (2.7)	6 (1.6)	0.29 (0.11-0.78)
					P_{trend} < 0.01

*Adjusted for age, sex, education, and biliary stone status.
† Adjusted for age and sex.
‡ Data on aspirin use not available for one population control and one gallbladder cancer case.

retrograde cholangiopancreatography), medical record review, and interview. Any participant who reported a prior cholestectomy or a history of gallstones was defined as having had biliary stones. For controls, such status was determined based on interviews and abdominal ultrasound. Approximately 85% of the population controls consented to ultrasound screening for the detection of asymptomatic stones.

Statistical Analysis. Unconditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI) to estimate the association of aspirin use with cancer risk at each anatomic subsite independent of potential confounding variables (age, sex, biliary stone status, and education). Other putative risk factors for biliary tract cancer, including obesity, diabetes, cigarette and alcohol use, and tea consumption, were not considered to be potential confounding variables, having no apparent relationship with aspirin use. The risk of biliary stones associated with aspirin use was also estimated, controlling for age, sex, and education. All population controls were used for comparison with bile duct or ampullary cancer cases, population controls without cholecystectomy with gallbladder cancer cases, and population controls without stones with biliary stone cases. Tests for linear trend in risk according to ordinal scales of each exposure variable were conducted to assess possible dose-response relationships. Our analysis excluded two subjects (one population control and one with gallbladder cancer) who did not furnish any information on aspirin use. Statistical analyses were done using SAS software, version 8.2 (SAS Institute, Cary, NC). All tests were two-sided, with $P < 0.05$ defined as statistically significant.

Results

More women than men were diagnosed with gallbladder cancer or biliary stones, whereas slightly more men than women were diagnosed with cancers of the bile duct or ampulla of Vater (Table 1). There was no difference in age or marital status between cancer cases and population controls, although biliary stone cases were younger and more likely to be married. Biliary stones were much more common among cases of biliary tract cancer, particularly of the gallbladder, than among population controls. Relative to population controls, gallbladder cancer cases had fewer years of education and a greater body mass index, and were more likely to have a history of diabetes and to consume tea but not cigarettes or alcohol regularly. Also, compared with population controls, those with bile duct and ampullary cancers were less likely to have a history of hypertension and more likely to smoke cigarettes, whereas biliary stone cases were less likely to have a history of hypertension or smoke cigarettes, and more likely to have a higher education, a greater body mass index, or a history of diabetes.

The prevalence of regular aspirin use among population controls was 5.7%, divided almost equally between former and current users (Table 2). Most users reported taking fewer than eight pills per week for <3 years. Compared with nonusers, aspirin users were generally older and more educated. After controlling for age, sex, education, and biliary stone status, aspirin use was associated with a 63% decreased risk of gallbladder cancer (OR, 0.37; 95% CI, 0.17-0.80), increasing to 77% for current users (OR, 0.23; 95% CI, 0.07-0.74). No statistically significant association with former aspirin use was observed. Also, relative to nonusers, those who started use at an earlier age, took aspirin more frequently ($P_{trend} = 0.02$) or for longer periods ($P_{trend} < 0.01$), were at a lower risk of gallbladder cancer. A stronger inverse relationship between aspirin use and gallbladder cancer risk was observed for older subjects (age ≥65: OR, 0.28; 95% CI, 0.10-0.77 versus age <65: OR, 0.58; 95% CI, 0.18-1.92; $P_{interaction} = 0.005$). Among the gallbladder cancer cases, 11 took aspirin regularly, all of whom had a history of biliary stones. Among the subset of cases and population controls who had biliary stones, the inverse relationship between aspirin use and gallbladder cancer risk persisted (OR, 0.44; 95% CI, 0.19-0.99).

A reduced risk of bile duct (OR, 0.48; 95% CI, 0.19-1.19) and ampullary (OR, 0.22; 95% CI, 0.03-1.65) cancer was associated with aspirin use, but these findings were based on small numbers and were not statistically significant. Given the limited number of cases with bile duct or ampullary cancer, risk estimates for these two subsites associated with frequency, timing, and duration of use are not presented in Table 2. No clear relationship was seen between aspirin use and biliary stones (OR, 0.92; 95% CI, 0.59-1.44).

Discussion

Data from this population-based study showed a significant 63% reduction in the risk of gallbladder cancer associated with

Table 2. ORs and 95% CIs for biliary tract cancer (by anatomic subsite) and biliary stones in relation to aspirin use

Extrahepatic bile duct		Ampulla of Vater		Biliary stone cases	
n (%)	OR* (95% CI)	*n* (%)	OR* (95% CI)	*n* (%)	OR† (95% CI)
185 (96.9)	1.00	67 (98.5)	1.00	990 (95.5)	1.00
6 (3.1)	0.48 (0.19-1.19)	1 (1.5)	0.22 (0.03-1.65)	47 (4.5)	0.92 (0.59-1.44)
				27 (2.6)	0.88 (0.50-1.57)
				20 (1.9)	0.97 (0.49-1.91)
				25 (2.4)	0.89 (0.48-1.65)
				20 (1.9)	0.88 (0.46-1.67)
				32 (3.1)	0.80 (0.48-1.35)
				13 (1.3)	1.33 (0.54-3.26)
					$P_{trend} = 0.96$
				17 (1.6)	0.66 (0.34-1.30)
				30 (2.9)	1.17 (0.65-2.11)
					$P_{trend} = 0.97$

aspirin use. Despite the low prevalence of aspirin use in the study population, this inverse relationship was evident with respect to frequency, timing, and duration of use. In addition, there was a nonsignificant reduction in the risk of bile duct and ampullary cancers, but no association with biliary stones.

Our results are similar to those of a U.S.-based case-control study that found a borderline inverse association between regular NSAID use and gallbladder cancer risk (OR, 0.5; 95% CI, 0.3-1.1) with suggestive evidence of a greater reduction in risk for long-term users (6). However, that study did not examine aspirin use separately, was based on 125 cancer cases, and did not account for potential confounding by gallstones, a major risk factor for gallbladder cancer.

In our study, the inverse association between aspirin use and gallbladder cancer persisted after adjusting for biliary stone status. The prevalence of biliary stones among gallbladder cancer cases was 81%. Because all cases who used aspirin regularly had biliary stones, we could only evaluate the effect of aspirin on gallbladder cancer among individuals with stones. Restricting the analysis to cases with stones, aspirin use remained associated with reduced risk of gallbladder cancer (OR, 0.44). Among both cancer cases and controls who had biliary stones, a larger proportion of the controls took aspirin (9.0% versus 3.7%), and for a longer average duration (37.3 versus 19.3 months), than did the cases. Our observations suggest that aspirin lowers the risk of gallbladder cancer associated with gallstones, perhaps by inhibiting inflammatory processes involved in biliary carcinogenesis (3), whereas aspirin has little or no effect on the risk of gallstones.

An inverse relationship between aspirin use and risk of gallbladder cancer (and perhaps bile duct and ampullary cancers) is consistent with the protective effects of NSAIDs observed for colorectal and probably other cancers of the gastrointestinal tract (1, 2). Although the exact mechanisms are unclear, the effect of NSAIDs may be related to decreased prostaglandin synthesis by inhibition of the cyclooxygenase (COX) enzyme, especially the COX-2 isoform, which is induced by proinflammatory and mitogenic factors (7). COX-2 expression is elevated in human gallbladder cancer relative to normal tissue (8) and with advancing tumor stage (9, 10). Expression of COX-2 is also increased in bile duct cancer and in primary sclerosing cholangitis, an inflammatory precursor condition, relative to normal tissue (11). Whereas the role of COX-2 in ampulla of Vater cancer is less clear, a recent study showed no difference in measures of cell proliferation, apoptosis, and angiogenesis between COX-2–positive and COX-2–negative tumors (12).

Although some clinical investigations and one observational study have suggested that NSAIDs may inhibit gallstone formation (13-18), our finding of no association is consistent with two population studies that reported no difference in hospitalization for gallstone disease (19) or in gallstone prevalence (20) between users and nonusers of aspirin or NSAIDs. Future prospective studies examining the timing of NSAID use with respect to gallstone diagnosis are needed.

Our population-based study, with a relatively large accrual of cases of this rare cancer, had the benefits of pathologic and clinical review to confirm tumor histology and anatomic subsite classification, detailed assessment of biliary stone status, strict quality control standards for data collection, and high participation among cases and controls, thus minimizing the potential for misclassification and selection bias. However, several limitations of the study should be noted. Foremost, the prevalence of aspirin use was low (5%), reducing the statistical power to examine the relationship between aspirin use and subsites of biliary tract cancer, particularly of the bile duct and ampulla of Vater. In China, aspirin is mainly used as an over-the-counter medication for occasional pain relief and is seldom taken on a regular basis for cardiovascular disease prevention. Second, aspirin use was assessed by self-report, without validation by medical record review, but recall bias between cases and controls may be countered by the small percentage of subjects who reported long-term aspirin use or who suspected any link between aspirin use and biliary tract cancer. Finally, data on the use of NSAIDs other than aspirin were not ascertained to evaluate their potential effects on cancer risk.

In summary, data from this population-based study revealed that aspirin use lowers the risk of biliary tract cancers, especially of the gallbladder, perhaps by inhibiting the inflammatory pathways involved in biliary carcinogenesis. Further studies of biliary tract cancer in other populations are warranted to replicate our findings and gain insights into mechanisms underlying the reduced risks associated with use of aspirin and possibly other NSAIDs.

Acknowledgments

We thank the collaborating surgeons and pathologists in Shanghai for their assistance in patient recruitment and pathology review; Jiarong Cheng and Lu Sun of the Shanghai Cancer Institute for coordinating data collection; and Shelley Niwa, Hope Cohen-Webb, and Sara Glashofer of Westat, Inc. for study management and data processing.

References

1. Thun MJ, Henley SJ, Patrono C. Nonsteroidal anti-inflammatory drugs as anticancer agents: mechanistic, pharmacologic, and clinical issues. J Natl Cancer Inst 2002;94:252–66.
2. Gonzalez-Perez A, Garcia Rodriguez LA, Lopez-Ridaura R. Effects of non-steroidal anti-inflammatory drugs on cancer sites other than the colon and rectum: a meta-analysis. BMC Cancer 2003;3:28.
3. Wistuba II, Gazdar AF. Gallbladder cancer: lessons from a rare tumour. Nat Rev Cancer 2004;4:695–706.
4. Shaib Y, El Serag HB. The epidemiology of cholangiocarcinoma. Semin Liver Dis 2004;24:115–25.
5. Hsing AW, Gao YT, Devesa SS, Jin F, Fraumeni JF Jr. Rising incidence of biliary tract cancers in Shanghai, China. Int J Cancer 1998;75:368–70.
6. Coogan PF, Rosenberg L, Palmer JR, et al. Nonsteroidal anti-inflammatory drugs and risk of digestive cancers at sites other than the large bowel. Cancer Epidemiol Biomarkers Prev 2000;9:119–23.
7. Zha S, Yegnasubramanian V, Nelson WG, Isaacs WB, De Marzo AM. Cyclooxygenases in cancer: progress and perspective. Cancer Lett 2004;215:1–20.
8. Ghosh M, Kawamoto T, Koike N, et al. Cyclooxygenase expression in the gallbladder. Int J Mol Med 2000;6:527–32.
9. Asano T, Shoda J, Ueda T, et al. Expressions of cyclooxygenase-2 and prostaglandin E-receptors in carcinoma of the gallbladder: crucial role of arachidonate metabolism in tumor growth and progression. Clin Cancer Res 2002;8:1157–67.
10. Kawamoto T, Shoda J, Asano T, et al. Expression of cyclooxygenase-2 in the subserosal layer correlates with postsurgical prognosis of pathological tumor stage 2 carcinoma of the gallbladder. Int J Cancer 2002;98:427–34.
11. Hayashi N, Yamamoto H, Hiraoka N, et al. Differential expression of cyclooxygenase-2 (COX-2) in human bile duct epithelial cells and bile duct neoplasm. Hepatology 2001;34:638–50.
12. Kim HJ, Sohn TS, Lee KT, et al. Expression of cyclooxygenase-2 and its correlation with clinicopathologic factors of ampulla of vater cancer. J Korean Med Sci 2003;18:218–24.
13. Attili AF, Capocaccia R, Carulli N, et al. Factors associated with gallstone disease in the MICOL experience. Multicenter Italian study on epidemiology of cholelithiasis. Hepatology 1997;26:809–18.
14. Broomfield PH, Chopra R, Sheinbaum RC, et al. Effects of ursodeoxycholic acid and aspirin on the formation of lithogenic bile and gallstones during loss of weight. N Engl J Med 1988;319:1567–72.
15. Das A, Baijal SS, Saraswat VA. Effect of aspirin on gallbladder motility in patients with gallstone disease. A randomized, double-blind, placebo-controlled trial of two dosage schedules. Dig Dis Sci 1995;40:1782–5.
16. Hood K, Gleeson D, Ruppin DC, Dowling RH. Prevention of gallstone recurrence by non-steroidal anti-inflammatory drugs. Lancet 1988;2:1223–5.
17. Marks JW, Bonorris GG, Schoenfield LJ. Effects of ursodiol or ibuprofen on contraction of gallbladder and bile among obese patients during weight loss. Dig Dis Sci 1996;41:242–9.
18. Sterling RK, Shiffman ML, Sugerman HJ, Moore EW. Effect of NSAIDs on gallbladder bile composition. Dig Dis Sci 1995;40:2220–6.
19. Kurata JH, Marks J, Abbey D. One gram of aspirin per day does not reduce risk of hospitalization for gallstone disease. Dig Dis Sci 1991;36:1110–5.
20. Pazzi P, Scagliarini R, Sighinolfi D, et al. Nonsteroidal antiinflammatory drug use and gallstone disease prevalence: a case-control study. Am J Gastroenterol 1998;93:1420–4.